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Posted Date: August 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10350702/v1

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Additional Declarations: No competing interests reported.

The Impact of Food on the Bioavailability of Oral Anti-Cancer Tyrosine Kinase Inhibitors (TKIs) Approved Since 2000: A Systematic Review and Meta-Analysis of Crossover Trials

A Systematic Review Protocol

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Systematic review registration: PROSPERO CRD420261448103

Abstract

Background: Oral tyrosine kinase inhibitors (TKIs) have converted the management of numerous malignancies, but many are Biopharmaceutics Classification System (BCS) class II or IV compounds whose absorption is highly sensitive to co-administration with food. Reported food effects on maximum plasma concentration (Cmax) and area under the curve (AUC) range from negligible to several-fold changes, with direct implications for efficacy, toxicity, and dosing guidance.

Objectives: To quantify, for each FDA-approved oral anti-cancer TKI individually, the effect of food (and of meal fat/caloric content) on AUC and Cmax relative to the fasted state, and to explore population, dosing-condition, and physicochemical determinants of this effect.

Methods: This protocol was developed in accordance with the PRISMA-P 2015 statement and registered with PROSPERO. PubMed, Scopus, Embase, Web of Science, Google Scholar, and the FDA regulatory review databases will be searched from January 2000 to the end of 2025 for randomized or fixed-sequence crossover trials reporting AUC and/or Cmax under fed and fasted conditions. Two reviewers will independently screen studies, extract data in duplicate, and assess risk of bias with the extended Cochrane RoB 2 tool for crossover trials. Pharmacokinetic parameters will be analyzed on the log-transformed scale; where only arithmetic means and standard deviations are reported, Taylor-series approximations will be used to derive the corresponding log-scale statistics, and the standard error of the within-subject difference will be computed incorporating an imputed or reported within-subject correlation coefficient. Drug-specific random-effects and, where sufficient conditions are reported, network meta-analyses will pool the ratio of geometric means (RoGM) for AUC and Cmax; meta-regression will examine physicochemical and pharmacokinetic moderators.

Ethics and dissemination: No original patient data will be collected and formal ethics approval is not required. Findings will be disseminated through peer-reviewed publication and conference presentation and are intended to inform evidence-based food-intake recommendations for oral TKI administration.

Keywords: Anti-cancer tyrosine kinase inhibitors; Oral bioavailability; Food effect; Pharmacokinetics; Fed/fasted state; Crossover trial; Geometric mean ratio; Network meta-analysis

Systematic review registration: PROSPERO CRD420261448103.

1. Introduction

1.1 Clinical significance of oral tyrosine kinase inhibitors in oncology

Small-molecule tyrosine kinase inhibitors (TKIs) have become a cornerstone of precision oncology since imatinib's approval in 2001 (1). Oral TKIs now target driver kinases across a wide range of cancers (chronic myeloid leukemia, non-small-cell lung cancer, renal cell carcinoma, gastrointestinal stromal tumors, hepatocellular carcinoma, and others) (2,3). Compared with intravenous cytotoxic chemotherapy, the oral route is simply more convenient. It costs less to deliver, preserves quality of life, and has made chronic, outpatient management possible for diseases once treated only in infusion clinics (4,5). But this convenience comes at a price; Oral dosing introduces pharmacokinetic variabilities that intravenous agents largely avoid, since exposure depends not just on the dose given but, on the extent, and rate of gastrointestinal absorption, which is highly sensitive to conditions in the gut at the moment of ingestion, chief among them, whether or not food is present (6-8)

Unlike traditional cytotoxic agents, most TKIs are taken chronically. So small, repeated deviations in systemic exposure can lead to clinically meaningful differences in efficacy or toxicity over the course of treatment. TKIs are also typically approved at narrow, fixed oral doses derived from registration trials in which fed or fasted status was tightly controlled. Real-world administration looks nothing like that. Patients, caregivers, and even prescribers frequently receive inconsistent guidance on whether a given TKI should be taken with or without food (9). This gap between the controlled conditions of pivotal trials and the variability of everyday administration is the central clinical problem that motivates the present review.

1.2 Physiological mechanisms of food-drug interactions

Food can alter oral drug absorption through several physiological mechanisms, and these do not all pull in the same direction (10). Meal ingestion delays gastric emptying and prolongs gastric residence time. This extends the dissolution time available to poorly soluble compounds, but it can also expose acid-labile drugs to degradation. Fat-containing meals stimulate biliary and pancreatic secretion, raising luminal bile salt concentration and promoting micellar solubilization of lipophilic drugs, a mechanism that can markedly increase the fraction of drug dissolved and available for absorption (11). Meals also transiently raise gastric and duodenal pH, splanchnic blood flow, and mesenteric lymphatic flow, and can modulate the activity of intestinal efflux transporters (notably P-glycoprotein) and first-pass metabolizing enzymes (notably cytochrome P450 3A4). Each of these effects can independently raise or lower systemic exposure, depending on a given drug's specific transporter and enzyme affinities (9).

The net direction and magnitude of a food effect is therefore compound-specific, driven largely by the physicochemical properties of the drug in question. Under the Biopharmaceutics Classification System (BCS), high-solubility, high-permeability compounds (Class I) are typically less susceptible to clinically relevant food effects. Low-solubility compounds (BCS Class II and IV) are a different story, and many oral TKIs fall squarely into this category, disproportionately prone to food-enhanced dissolution and absorption (12). It is precisely this mechanistic heterogeneity across the TKI class that makes food effects impossible to generalize from one drug to the next, and why a drug-by-drug quantitative synthesis, rather than a single class-wide estimate, is what is actually needed to generate clinically actionable guidance.

1.3 Why Cmax and AUC fluctuations matter for TKI patient outcomes

AUC and Cmax are the two pharmacokinetic parameters most directly linked to clinical outcomes for TKIs. AUC, a measure of total systemic exposure, is frequently correlated with treatment

efficacy, since many TKIs must sustain plasma concentrations above a minimum effective threshold to maintain continuous target kinase inhibition. Cmax, by contrast, tracks more closely with acute, concentration-dependent toxicities, including gastrointestinal, hepatic, and cardiac adverse events reported for several agents in this class(13). TKIs are frequently characterized by a comparatively narrow therapeutic index and steep exposure-response relationships. Because of this, even moderate food-induced shifts in AUC or Cmax, in either direction, can move a patient from a sub-therapeutic to an adequately treated exposure range, or from a well-tolerated regimen to a toxicity-prone one.

The clinical stakes of this variability are illustrated by TKIs for which regulatory labeling explicitly restricts administration relative to meals. Some agents must be taken on an empty stomach because food substantially increases exposure and toxicity risk; others carry a recommendation for a low-fat meal specifically to avoid the excessive absorption seen with high-fat meals (9). Conversely, some TKIs show clinically important increases in bioavailability when taken with food, which raises the possibility that fasted administration in unselected, real-world populations could lead to systematic underdosing and reduced efficacy. Non-adherence to food-intake instructions is far from rare in oncology populations, particularly among older or medically complex patients managing several prescriptions at once (13). This means that the magnitude of a given TKI's food effect has direct, population-level relevance for treatment outcomes.

1.4 Rationale for a quantitative, drug-level synthesis

Food-effect data for individual TKIs are scattered across product-specific registration studies, regulatory review documents (FDA Clinical Pharmacology and Biopharmaceutics Reviews), and the published literature, and they are reported using inconsistent metrics, meal definitions, and population types (healthy volunteers versus patients with malignancies, single-dose versus steady-

state conditions)[1] (11). No existing systematic review has quantitatively synthesized food-effect magnitude across the full contemporary class of FDA-approved oral anti-cancer TKIs using harmonized meal definitions and a unified log-scale statistical framework, nor has any formally examined which physicochemical and pharmacokinetic properties (aqueous solubility class, calculated log P, dose, elimination half-life) predict the direction and magnitude of the effect. Addressing this gap through a rigorous, drug-specific meta-analytic synthesis, including network meta-analysis where three or more feeding conditions are available for the same drug, could generate practical, evidence-based food-intake recommendations, with the potential to reduce iatrogenic exposure variability across this widely prescribed drug class.

1.5 Objectives

This systematic review and meta-analysis aims to:

- Quantify, separately for each individual oral anti-cancer TKI, the effect of food intake on AUC and Cmax relative to the fasted state, using crossover trial data;
- Determine whether the fat and caloric content of the meal (low-fat versus high-fat, per standardized reference definitions) significantly modifies the magnitude of the food-drug interaction;
- Compare the pattern of food effect between healthy volunteers and patients with malignancies, and between single-dose and steady-state dosing conditions;
- Examine, via meta-regression, how physicochemical and pharmacokinetic properties of individual TKIs correlate with the magnitude and direction of the observed food effect.

2. Methods

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement (see accompanying PRISMA-P checklist) (14) and Cochrane Handbook methodology (15), and the completed systematic review will be reported in accordance with PRISMA 2020 (16). The protocol has been registered with PROSPERO.

2.1. Eligibility criteria

Eligibility was defined a priori using the PICOS framework (Table 1).

Table 1. Eligibility criteria (PICOS).

PICOS element	Criterion
Population	Adults (≥18 years) with malignancies, or healthy adult volunteers, receiving an FDA-approved oral TKI (approved since 2000) in a trial directly comparing fed vs. fasted administration. Pediatric-only studies excluded (summarized narratively).
Intervention	Standard therapeutic or protocol-specified oral TKI dose following a high-fat and/or low-fat meal, single-dose or steady-state. Meal composition extracted quantitatively (kcal, grams of fat) and classified against FDA reference standards (17) (high-fat: ~800–1000 kcal, ~50% calories from fat; low-fat: ~400–500 kcal, ~25% calories from fat).
Comparator	Identical TKI, formulation, and dose under fasting conditions (typically ≥8-10 hour overnight fast) within the same crossover trial.
Outcomes	Primary: Ratio of Geometric Means (RoGM, fed/fasted) for AUC (0-t preferred; 0-∞ where 0-t unavailable; 0-τ at steady state) and Cmax. Secondary: RoGM differences by meal type, population, and dosing condition; meta-regression associations; exploratory adverse-event incidence.
Study design	Included: human randomized or fixed-sequence crossover trials reporting AUC and/or Cmax under both fed and fasted conditions. Excluded: parallel-group trials; animal/in vitro studies; PBPK modeling without original clinical PK data; studies with differing formulation between periods; pediatric-only studies.

Studies were further required to be conducted in the clinical pharmacology/Phase I setting, including both dedicated healthy-volunteer food-effect bioavailability studies and food-effect sub-

studies embedded within oncology treatment trials, with no restriction by country or healthcare setting.

2.2. Information sources and search strategy

Comprehensive searches will be performed in PubMed, Scopus, Embase, Web of Science, and Google Scholar, from January 2000 to the end of 2025. The FDA Drugs@FDA database (Clinical Pharmacology and Biopharmaceutics Reviews) will additionally be searched to capture unpublished or regulatory-only food-effect data. Search terms will combine the generic names of all FDA-approved oral anti-cancer TKIs with the terms "food effect," "fed," "fasting," "bioavailability," and "pharmacokinetics." Backward and forward citation searching of included studies will be performed, and study authors or subject-matter experts will be contacted where key data appear to be missing. No restrictions on language or publication status will be applied; non-English records will be translated as needed.

2.3. Study selection

Two reviewers will independently screen titles and abstracts, and subsequently full texts, against the eligibility criteria using EndNote, with disagreements resolved by discussion or adjudication by a third reviewer. Study selection will be documented and reported using a PRISMA 2020 flow diagram in the final review.

2.4. Data extraction (data items)

Data will be extracted in duplicate using a piloted, standardized extraction form capturing: drug name, dose, formulation, population type, sample size, study design (randomized/fixed-sequence), meal type and quantitative composition (kcal, grams of fat), dosing condition (single-dose/steady-state), washout duration relative to the drug's elimination half-life, AUC/Cmax type and summary

statistics (arithmetic or geometric mean, SD/CV, sample size per period), and the reported within-subject correlation coefficient where available. Discrepancies will be resolved by consensus or adjudication by a third reviewer.

2.5. Risk of bias assessment

Risk of bias will be assessed using the extended Cochrane Risk of Bias 2 (RoB 2) tool (18) for crossover trials, with particular attention to carry-over effects and the adequacy of the washout period relative to each drug's elimination half-life. Assessment will be performed independently in duplicate, with disagreements resolved by consensus or a third reviewer.

2.6. Statistical analysis and data synthesis

Pharmacokinetic data (AUC and Cmax) characteristically display positive skewness consistent with a log-normal distribution; accordingly, all effect-size calculations will be conducted on the log-transformed scale, with the Ratio of Geometric Means (RoGM) as the primary effect measure. For studies reporting only arithmetic means and standard deviations, the corresponding log-scale mean and variance will be recovered analytically using a Taylor-series (method-of-moments) approximation, under the assumption that the underlying data follow a log-normal distribution:

$$X_{log} = ln(X) - \frac{1}{2} ln\left(1 + \frac{SD^2}{X^2}\right) \quad (1)$$

$$SD_{log}^2 = ln\left(1 + \frac{SD^2}{X^2}\right) \quad (2)$$

where $\bar{X}$ and SD are the reported arithmetic mean and standard deviation of the pharmacokinetic parameter (AUC or Cmax) in a given feeding condition, and $\bar{X}_{log}$ and SD_{log}^2 are the corresponding mean and variance on the natural-log scale used in all subsequent pooling.

Because crossover designs induce intra-individual correlation between the fed and fasted measurements taken in the same subjects (19,20), the variance and standard error of the within-subject difference in log-transformed AUC/Cmax will be computed as:

$$SE_{diff} = \sqrt{SE_{fed}^2 + SE_{fasted}^2 - 2r \cdot SE_{fed} \cdot SE_{fasted}} \quad (3)$$

where SEfed and SEfasted are the standard errors of the log-scale means under each feeding condition, and r is the within-subject (period-to-period) correlation coefficient. Where r is not reported by the primary study, it will be imputed using a standard value, with robustness evaluated through pre-specified sensitivity analyses across a plausible range:

$$r = 0.5,\ r \in [0.3, 0.7]\ (sensitivity\ range) \quad (4)$$

Primary analyses will be conducted separately for each individual TKI; pooling across pharmacologically distinct drugs will not be performed in the primary analysis. A random-effects model (REML estimation, with Hartung–Knapp–Sidik–Jonkman adjustment applied where few studies are available per comparison) using inverse-variance weighting will pool the log-scale RoGM for AUC and Cmax within each drug, with results back-transformed and reported as geometric mean ratios with 95% confidence intervals. Where three or more feeding conditions are reported for the same drug (fasting vs. low-fat vs. high-fat meal), a network meta-analysis will be used to enable indirect and multi-condition comparisons; transitivity will be assessed by comparing the distribution of effect modifiers (dose, population, dosing condition) across comparisons, and consistency will be evaluated via node-splitting and design-by-treatment interaction models.

Cross-drug pooling will only be explored through meta-regression, using physicochemical and pharmacokinetic covariates (aqueous solubility class per the Biopharmaceutics Classification

System, calculated log P, therapeutic dose, elimination half-life) as moderators, in order to formally address objective 4. Heterogeneity will be quantified using I^2, τ^2, and 95% prediction intervals. Publication bias and small-study effects will be assessed via funnel plots and Egger's test (or comparison-adjusted funnel plots for network estimates) wherever ≥10 studies contribute to a given comparison. All analyses will be conducted in R using the meta, metafor, and netmeta packages.

2.7. Confidence (certainty) assessment

Confidence in pooled pairwise estimates will be assessed using the GRADE framework (21) across its standard domains (risk of bias, inconsistency, indirectness, imprecision, and publication bias). For network meta-analysis comparisons, the CINeMA (Confidence in Network Meta-Analysis) framework (22) will additionally be applied. Sensitivity analyses around the imputed within-subject correlation coefficient (r), and around alternative handling of the AUC-type hierarchy and single-dose versus steady-state stratification, will further inform robustness judgments.

2.8. Subgroup and sensitivity analyses

- Healthy volunteers vs. patients with malignancies
- Single-dose vs. steady-state dosing
- Low-fat vs. high-fat meal, per the standardized reference definitions
- TKI generation (first vs. second/third-generation), where clinically meaningful-exploratory

3. Discussion

This will be, to our knowledge, the first systematic review to quantitatively synthesize food-effect data across the full contemporary class of FDA-approved oral anti-cancer TKIs using harmonized meal definitions, a unified log-scale statistical framework appropriate for the log-normal distribution of pharmacokinetic data, and formal exploration of physicochemical and pharmacokinetic predictors of effect magnitude via meta-regression. By deliberately analyzing each TKI separately rather than pooling across a mechanistically heterogeneous drug class, and by supplementing published literature with regulatory review data from the FDA and EMA, the review is designed to generate drug-specific, clinically actionable estimates rather than a single, potentially misleading class-wide average.

Anticipated limitations include the possibility that within-subject correlation coefficients will be unreported for a substantial proportion of included studies, necessitating imputation; this is addressed through pre-specified sensitivity analyses across a plausible correlation range. Heterogeneity in meal composition reporting, in AUC truncation methods, and in population type (healthy volunteers versus oncology patients) may also limit comparability across studies for some drugs; standardized meal classification and pre-specified subgroup analyses are intended to mitigate, though not eliminate, this source of variability. For TKIs with only a single available food-effect study, precision of drug-specific estimates will necessarily be limited, and such findings will be interpreted accordingly.

4. Declarations

Ethics approval and consent to participate 4.1

Not applicable. This is a protocol for a systematic review and meta-analysis of previously published and publicly available regulatory data; no original human participant data will be collected.

4.2. Consent for publication

Not applicable.

4.3. Availability of data and materials

The data extraction form, extracted dataset, and analysis code developed for this review will be made available upon reasonable request to the corresponding author, and, where appropriate, deposited in a public repository at the time of publication of the completed review.

4.4. Funding

This review received no specific funding.

4.5. Conflicts of interest

The authors declare no conflicts of interest.

4.6. Author contributions

A.B. conceived and designed the review, drafted the protocol, and will act as guarantor. M.M., S.S., S.R., and M.A. contributed to protocol development and will contribute to screening, data extraction, and risk-of-bias assessment. All authors read and approved the final protocol.

4.7. Dissemination plans

Results will be submitted for publication in a peer-reviewed journal and presented at relevant oncology and clinical pharmacology conferences.

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